UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/508,932	09/24/2004	Jeffrey P. Demuth	31169-705.831	9878

21971 7590 10/10/2008

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER	
MYERS, CARLA J	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
10/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/508,932	DEMUTH ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-89* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,7,10-17,19,20,23-30,32,33,36-43,45,46,49-52,57, and 82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/13/07, 8/15/06, 2/25/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 5,8,9,18,21,22,31,34,35,44,47,48,53-56,58-81 and 83-89.

DETAILED ACTION

1. With respect to the Notice of an Informal or Non-Responsive amendment (NINA) of April 30, 2008, the NINA has been vacated in view of the interview summary of May 22, 2008 and the telephonic election of May 20, 2008.

Election/Restrictions

2. Applicant's election with traverse of Group I, and the combination of genes of ABCC5, GTF2H2 and ERCC2 in the reply filed on February 29, 2008 and in the telephone interview of May 20, 2008 is acknowledged. It is noted that the invention of Group VI (claim 57) has been rejoined with the elected invention, to the extent that claim 57 encompasses methods for identifying an agent by assaying for the level of the polynucleotides of each of ABCC5, GTF2H2 and ERCC2.

The traversal is on the ground(s) that it would not require undue burden to search a genus claim such as claim 82, which recites the detection of any combination of one or more of the 15 recited genes. This is not found persuasive because it is maintained that undue burden would be required to examine the significantly large number of distinct combinations encompassed by the claims. For example, claim 82 requires the examination of the 15 recited individual genes, all possible combinations of two of the 15 genes (ERCC2 and ERCC3, ERCC2 and LIG1, ERCC2 and ACTB, ERCC2 and XPC, etc), all possible combinations of three of the 15 genes (ERCC2, ERCC3 and LIG1; ERCC2, ERCC3 and ACTB; ERCC2, ERCC3 and XXPC, etc), all possible combinations of 4 of the 15 genes, all possible combinations of 5 of the 15 genes, etc. A search for the individual genes and each of the distinct combinations of genes are not

co-extensive with one another. Undue burden would be required to search the various individual and combinations of genes since such a search would require a search of the significantly large sequence databases, as well as a search of the literature for the genes and their association with cancer. Further, many genes have more than one name, further compounding the search burden. Also, many published references disclose gene expression data within tables and figures, and this information is frequently not indexed in sequence databases or even with the abstracts of papers. An additional search burden is required to analyze the contents of tables and figures in order to determine if a gene is novel or unobvious over the prior art, and or if the prior art discloses an association between expression of a gene and cancer. Therefore, it is maintained that it would require an undue burden to search and examine each of the patentably distinct genes and combinations of genes recited in Tables 1 and 5.

The response further asserts that the corresponding feature of each of the inventions is the correlation of expression levels of the markers of Table 1 and 5 in the diagnosis or in assessing anti-cancer therapeutics. This argument has also been fully considered but is not persuasive. Each of the claimed inventions does not require diagnosis and assessment of anti-cancer therapies. Rather, the invention of Group VII is directed to only a hybridization template and the invention of Group VIII is directed to a computer system. The inventions of Groups I and II require the analysis of distinct molecules – i.e., nucleic acids and proteins - which do not share both a common structure and activity. Further, the methods of inventions III, IV, V, and VIII do not share the technical feature of assessing anti-cancer therapies because the claims of

inventions III, IV, V, and VIII do not require performing such a method step. The only common feature to each of the recited inventions is the genes themselves or the proteins encoded by said genes. However, the genes recited in Tables 1 and 5, and particularly the genes of ABCC5, GTF2H2 and ERCC2, were well known in the art at the time the invention was made and thereby do not constitute a special technical feature that provides a contribution over the prior art. Additionally, the technical feature of general methods of identifying agents that can be used to treat cancer were known in the art at the time the invention was made. See, for example, Scherf et al (Nature Genetics. 2000; cited in the IDS of 8/13/07), Zembutsu et al (Cancer Research 2002; cited in the IDS of 8/13/07), and Zupi (U.S. Patent No. 6,080,727; cited in the IDS of 2/25/05).

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1-89 are pending.

Claims 5, 8, 9, 18, 21, 22, 31, 34, 35, 44, 47, 48, 53-56, 58-81 and 83-89 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 1-4, 6, 7, 10-17, 19, 20, 23-30, 32, 33, 36-43, 45, 46, 49-52, 57 and 82 have been examined herein to the extent that the claims read on the elected invention which requires determining the level of expression of the combination of ABCC5, GTF2H2 and ERCC2 by assaying for the level of said nucleic acids. The subject matter of the additional genes recited in Tables 1 and 5 and the subject matter of assaying for protein levels is withdrawn from consideration as being drawn to a non-elected invention.

Claim Objections

4. Claims 1, 7, 10-14, 20, 23-27, 33, 36-40, 46, 49-52, 57 and 82 are objected to because the claim includes subject matter of the non-elected inventions, namely the genes and combinations of genes other than the combination of the ABCC5, GTF2H2 and ERCC2 genes, and the determination of the level of protein by detecting proteins.

Claim Rejections - 35 USC § 112 second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6, 7, 10-13, 20, 33, 40-43, 45, 46, 49-52, 57 and 82 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4, 6, 7, 10-13, 40-43, 45, 46, 49-52 and 82 are indefinite over the recitation of "certain level." The specification and claims do not define this phrase and there is no art recognized definition for this phrase as it pertains to levels of expression. Accordingly, one of skill in the art cannot determine the meets and bounds of the claimed subject matter.

Claims 1-4, 6, 7, and 10-13 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the steps that permit the determination of the effect of an agent on gene expression or on proliferation or death of a cancer cell. The claims recite only method steps of determining gene

expression levels in a cancer cell and identifying an agent as reducing proliferation or causing death of the cancer cells based on gene expression levels. However, the claims do not recite any relationship between the agent and gene expression levels or between the agent and cell proliferation or death, such as step of treating the cancer cells with an agent and then determining gene expression levels or determining cell proliferation or death. Thereby, the claims omit the essential steps required to identify an agent as useful for reducing the proliferation of cancer cells or causing death of cancer cells.

Claim 2 is indefinite over the recitation of “said tow or more makers” because this phrase lacks proper antecedent basis.

Claims 7, 20, 33, and 46 are indefinite over the recitation of "expanded group of genes represented by genes” because it is not clear as to what is intended to be meant by genes being represented by genes. This phrase is not defined in the specification or claims and there is no art recognized definition for this phrase. It is unclear, for example, whether the represented genes are the same as, part of, homologues of, or in some way similar to the expanded group of genes.

Claims 7, 20, 33 and 46 are also indefinite over the recitation of “positively or negatively associated” because the claims do not set forth what the genes are associated with.

Claims 7, 20, 33 and 46 are indefinite over the recitation of IGEI. The specification does not provide a clear definition for this term, the claims do not define this term and there is no art recognized definition for this term. The specification (page 50) provides an example of an IGEI, stating that “(t)hese data were combined into

interactive gene expression indices (IGEI) by placing one ore more genes directly associated with the phenotype in the numerator and one or more genes negatively associated with the genotype in the denominator using the quantitative reverse transcriptase-PCR method described in Willey." However, this example is not considered to constitute a limiting definition for the term "IGEI." In the absence of a clear definition for this phrase, one of skill in the art cannot determine the meets and bounds of the claimed invention.

Claim 20 is also indefinite over the recitation of the negatively associated genes. While the claim previously refers to evaluating positively associated genes, the claim does not previously refer to negatively associated genes. Thereby, it is unclear as to what constitutes the negatively associated genes.

Claim 57 is indefinite because the claim does not recite a clear nexus between the preamble of the claim and the final step of the claim. The claim is drawn to a method of screening for an agent capable of modulating the onset or progression of cancer. However, the final step is one of comparing a first and second IGEI. The claims do not set forth how comparing a first and second IGEI results in the determination that an agent modulates the onset or progression of cancer.

Claim Rejections - 35 USC § 112 - Enablement

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 7, 10-17, 19, 20, 23-30, 32, 33, 36-43, 45, 46, 49-52, 57 and 82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

Claims 1-4, 6, 7, 10-13 and 82 are drawn to a method for determining whether an agent can be used to reduce proliferation or cause cell death of cancer cells or inhibit growth of cancer cells comprising quantifying the level of expression of the markers ABCC5, GTF2H2 and ERCC2 by assessing the level of ABCC5, GTF2H2 and ERCC2 polynucleotides in a cancer cell, and identifying that an agent can be used to reduce proliferation, cause cell death or inhibit growth of cancer cells when the markers are expressed at “a certain level.” The claims and specification do not define the "certain level" of expression that is required to determine if an agent can reduce proliferation, cause cell death or inhibit growth of a cancer cell.

Claims 14-17, 19, 20, and 23-26 are drawn to a method for determining if an agent is effective for treating cancer comprising exposing cancer cells to an agent, quantifying the level of expression of the markers ABCC5, GTF2H2 and ERCC2 by assessing the level of ABCC5, GTF2H2 and ERCC2 polynucleotides in the cancer cell exposed to an agent and in cancer cells not exposed to an agent, and identifying an agent as effective for treating cancer if expression of the marker genes is altered in the presence of the agent. The claims thereby include methods wherein either an increase or a decrease (to any degree) in the level of the polynucleotides is indicative of an agent that can effectively treat cancer.

Claims 27-30, 32, 33, and 36-39 are drawn to a method for determining whether treatment with an agent should be continued in a cancer patient comprising obtaining two or more samples comprising cancer cells from a patient during course of treatment, quantifying the level of expression of the markers ABCC5, GTF2H2 and ERCC2 by assessing the level of ABCC5, GTF2H2 and ERCC2 polynucleotides in the two or more samples, and continuing treatment if the level of expression of at least one of the markers is not "significantly altered" during the course of treatment. Thereby, no change in expression of the ABCC5, GTF2H2 and ERCC2 genes appears to indicate an effective treatment.

Claims 40-43, 45, 46, and 49-52 are drawn to a method for identifying a new cancer treatment comprising quantifying the level of expression of the markers ABCC5, GTF2H2 and ERCC2 by assessing the level of ABCC5, GTF2H2 and ERCC2 polynucleotides in a sample of cancer cells, exposing the sample of cancer cells to an

agent, and identifying an agent as effective for treatment if at least one of the marker genes is expressed at “a certain level." Again, the claims and specification do not define the "certain level" of expression that is required to determine if an agent can reduce proliferation, cause cell death or inhibit growth of a cancer cell.

Claim 57 is drawn to a method for identifying an agent that modulates onset of non small cell lung cancer (NSCLC) or an agent that modulates progression of NSCLC comprising preparing a first IGEI for a population of NSCLC cells comprising expression levels of ABCC5, GTF2H2 and ERCC2, exposing the NSCLC cells to the agent, preparing a second IGEI for the cells exposed to the agent, and comparing the first and second IGEIs.

With the exception of claim 57, the claims encompass methods in which any type of cancer cell is analyzed to identify an agent for treating cancer.

Claims 13, 26, 39 and 52 are limited to methods wherein the agent is cisplatin, whereas the remaining claims encompass methods wherein the agent is any compound, any chemotherapeutic compound or any platinum compound.

Claim 3 requires that ABCC5, GTF2H2 and ERCC2 are miRNAs and claims 16, 29, and 42 require that ABCC5, GTF2H2 and ERCC2 are siRNAs.

The claims also encompass methods wherein the level of DNA is determined as a function of gene expression levels, such that the claims include detecting a change in gene copy number.

Nature of the Invention

The claims are drawn to methods for methods for identifying agents for treating cancer by assaying for the level of gene expression. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification teaches the results of a study in which gene expression levels were assayed in NSCLC cell lines having previously determined ranges of sensitivity to cisplatin (page 48). Comparisons were made between mRNA levels of ABCC5, GTF2H2 and ERCC2 in cisplatin sensitive cells and in cisplatin resistant cells. As stated in the specification (pages 48-49), "Data were obtained in the form of target gene molecules relative to 10^6 β-actin (ACTB molecules). To cancel the effect of ACTB variation among the different cell [sic] lines individual gene expression values were incorporated into ratios of one gene to another. Each two-gene ratio was compared as a single variable to chemoresistance for each of eight NSCLC cell lines using multiple regression. Following validation, single variable models best correlated with chemoresistance ($p < 0.001$), were determined."

The results for the correlation between individual gene expression levels and cisplatin chemoresistance in the NSCLC cell lines are provided in Table 3. It is stated that "(f)or 8/12 genes assessed, there was significant ($p<0.05$) correlation" (page 55). In particular, Table 3 indicates that ABCC5 and ERCC2 mRNA levels were correlated with

chemoresistance of NSCLC cell lines to cisplatin. GTF2H2 was not correlated with chemoresistance of NSCLC cell lines to cisplatin since GTF2H2 has an R^2 value of 0.02 and a p value of 0.7424. Accordingly, it is clear from the teachings in Table 3 and page 55 of the specification, that expression levels of GTF2H2 cannot be assayed alone to determine the effectiveness of cisplatin for the treatment of NSCLC.

The specification (page 50) teaches that data can be combined into interactive gene expression indices (IGEI) by placing one or more genes directly associated with the phenotype in the numerator and one ore more genes negatively associated with the genotype in the denominator.

The specification (page 55) further states:

"IGEI were established comprising every possible combination of the expression value of one gene divided by the expression value of another gene for data obtained from each of the initial eight NSCLC cell lines (Group 1). Each expression value was calculated as moleculesll0s ACTB molecules. Thus, in these IGEI the effect of the reference gene, ACTB, is cancelled. For example:

ERCC2 molecules/10^6 ACTB molecules + XPC molecules/ 10^6 ACTB molecules = ERCC2 molecules/XPC molecules.

In Table 4 (Figure 4), it is reported that the ratios of ERCC2/GTF2H2 and ABCC5/GTF2H2 were correlated with response to cisplatin in NSCLC cell lines, with R^2 values of 0.90 and 0.91, and p values of 0.0004 and 0.0002, respectively.

Working Examples:

The specification provides working examples in which the mRNA levels of ABCC5, GTF2H2 and ERCC2 are determined in cisplatin resistant and cisplatin sensitive NSCLC cells.

The specification does not provide any working examples in which an agent is identified as being effective for reducing proliferation of cancer cells, causing death of cancer cells, inhibiting growth of cancer cells, modulating the onset of NSCLC cancer or modulating progression of NSCLC cancer by determining the level of each of ABCC5, GTF2H2 and ERCC2.

The specification does not provide any working examples in which expression levels of ABCC5, GTF2H2 and ERCC2 are determined in cancer cells other than NSCLC cells.

The specification does not provide any working examples in which expression levels of ABCC5, GTF2H2 and ERCC2 are determined following exposure to any agent other than cisplatin.

The specification does not provide any working examples in which ABCC5, GTF2H2 and ERCC2 miRNA or siRNA are determined and quantified. There are no teachings in the specification or art which indicate that ABCC5, GTF2H2 and ERCC2 are miRNAs or siRNAs. Nor does the specification provide any working examples in which a change in the polynucleotide of DNA, and thereby a change in DNA copy number, is detected as indicative of the efficacy of an agent.

Amount of Direction or Guidance Provided by the Specification:

The present claims appear to require a known relationship between the expression levels of ABCC5, GTF2H2 and ERCC2 and the occurrence of cancer. However, the specification has not established such an association.

Rather, the specification has provided information regarding the level of expression of ABCC5, GTF2H2 and ERCC2 in NSCLC cells that are resistant or sensitive to cisplatin. The finding that ERCC2 molecules/10^6 ACTB molecules and ABCC2 molecules/10^6 ACTB molecules were correlated with NSCLC cell lines sensitive to cisplatin treatment does not allow one to generate a method for identifying new agents that are effective for treating cancer. That is, the teaching of an association between relative ABCC2 and ERCC2 mRNA levels in NSCLC cell lines resistant to cisplatin is not equivalent to a teaching that ABCC2 and ERCC2 mRNA levels are correlated with the occurrence of cancer or that ABCC2 and ERCC2 mRNA levels are predictive of a patient's response to treatment with any agent.

Regarding claims 1-4, 6, 7, 10-13, 40-43, 45, 46, 49-52 and 82, the specification does not teach any "certain level" of mRNA that indicates that an agent is effective for treating cancer. There is no guidance provided in the specification as to particular thresholds of expression levels which indicate that a cell is responsive to treatment or is not responsive to treatment. Accordingly, the specification has enabled one of skill in the art to practice these claims because the specification does not teach or provide sufficient guidance as to how to determine a particular level of gene expression of ABCC5, GTF2H2 and ERCC2 which indicates that an agent has the effect of reducing proliferation, causing death of cancer cells and/or inhibiting growth of cancer.

Regarding claims 14-17, 19, 20, and 23-26, these claims require a comparison of ABCC5, GTF2H2 and ERCC2 polynucleotide levels before and after treatment of a cancer cell with an agent. Thereby, these claims require identifying an agent that either increases or decreases the expression of ABCC5, GTF2H2 and ERCC2. The specification (page 25) states that "Although some of the present (IGEI) marker sets can be expressed in non-treated cancer cells, treatment with an agent may, or may not, alter expression." However, the specification does not teach the level of ABCC5, GTF2H2 and ERCC2 expression in treated and non-treated cancer cells. The specification has not established that a change in the expression level of ABCC5, GTF2H2 and ERCC2 occurs in response to treatment with an agent and that either an increase or decrease in ABCC5, GTF2H2 and ERCC2 expression is correlated with effectiveness of cancer treatment.

Regarding claims 27-30, 32, 33, and 36-39, these claims require that, if during the course of treatment, there is no significant increase or decrease in ABCC5, GTF2H2 and ERCC2 expression levels, then treatment is continued. These claims also require knowledge of an association between expression levels of ABCC5, GTF2H2 and ERCC2 and the effectiveness of any type of therapy. However, again, the specification has not established such an association. Alternatively, these claims may be interpreted as including methods in which one concludes that therapy is effective because there is no change in expression levels and thereby one continues the therapy, as opposed to selecting an alternative therapy. In this situation, the claims infer that no change in expression levels correlates with an effective therapy. However, the specification has

not established that an absence of a change in the expression levels of ABCC5, GTF2H2 and ERCC2 is correlated with a positive response to all types of cancer therapy.

Regarding claim 57, this claim requires comparing any interactive gene indices (IGEI) prior to and after treatment with an agent, comparing the IGEIs and making a determination that an agent modulates (i.e., reduces or enhances) onset or progression of NSCLC. The claim does not set forth how the IGEI is determined. While the specification (page 50) indicates that IGEIs may be expressed as a ratio wherein the gene associated with the phenotype is the numerator and the gene not associated with the phenotype is the denominator. However, the specification does not provide sufficient guidance as to additional interactive indices of expression that can be determined to evaluate the effectiveness of a drug. Further, the specification does not provide sufficient guidance as to how to perform the method of claim 57, without undue experimentation, because the specification has not established that either an increase or a decrease in the level of expression of ABCC5, GTF2H2 and ERCC2 in response to treatment with an agent is correlated with a reduction or an enhancement in the onset of NSCLC or a reduction or increase in the progression of NSCLC.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The art of determining an association between gene expression levels and a phenotype, such as responsiveness to treatment, is highly unpredictable. Knowledge that gene expression levels are correlated with response to one type of therapy, such as cisplatin, does not allow one to predict whether gene expression levels will be correlated

with other types of therapy, such as radiation or antibody or antisense therapy. Further, knowledge that gene expression levels are altered in one type of cancer does not allow one to conclude which, if any, additional cancers will also be associated with a change in gene expression. Moreover, a finding that a change in gene expression levels are correlated with cell death or inhibition of proliferation does not allow one to conclude that the gene expression levels are also correlated with the onset of cancer, such that one could reasonable extrapolate the findings regarding an agent's ability to inhibit proliferation of cancer or to cause cell death to an agent's ability to prevent the onset of cancer.

The unpredictability of using gene expression levels to identify an agents to treat cancer is highlighted by the teachings in the specification wherein it is clearly disclosed that expression levels of GTF2H2 alone were not correlated with response of NSCLC cells to cisplatin treatment. Note that each of the present claims requires determining the level of GTF2H2 polynucleotides in order to identify an agent that reduces cancer cell proliferation, inhibits cancer cell proliferation, causes cancer cell death or modulates onset or progression of cancer.

The teachings in the prior art and post-filing data art further highlight the unpredictability in the art of establishing an association between gene expression levels and the occurrence of cancer or responsiveness of cancer cells to therapy.

For example, Damia (European Journal of Cancer. 1998. 34: 1783-1788) teaches that ERCC2 (referred to therein as XPD) mRNA levels were not correlated with

sensitivity to cisplatin and melphalan in human cancer cell lines, including ovarian carcinoma, leukemia and colon cancer cell lines (page 1786 and abstract).

Young (Clinical Cancer Research. March 1999. 5: 673-680) studied ABCC5 (referred to therein as MRP5) mRNA levels in SCLC and NSCLC cell lines following treatment with 4 different chemotherapeutic agents. Young reported that "Interestingly, MRP5 mRNA levels in the cell lines showed a moderate, negative correlation with VP-16 resistance" (page 677, col. 2.). A weak, non-significant negative correlation with VCR resistance was also detected. There was no correlation observed between ABCC5/MRP5 mRNA levels and response to doxorubicin (DOX) or cis-diamminedichloroplatinum II (CDDP; see Table 3). Young also teaches that MRP5 mRNA levels varied between SCLC and NSCLC cell lines (page 677, col. 1). This suggests that there is no absolute level of ABCC5/MRP5 mRNA present in all cancer cell types and indicates that a particular "certain level" of gene expression cannot necessarily be detected as indicative of response to an agent.

Kool (Cancer Research. 1997. 57: 3537-3547) also analyzed ABCC5/MRP5 mRNA levels in human cancer cell lines sensitive or resistant to treatment with doxorubicin or cisplatin. Kool reported that ABCC5/MRP5 mRNA levels varied significantly between different types of human tissues (Table 2). Kool concluded that while ABCC5/MRP5 is overexpressed in some resistant cell lines, there is no clear correlation between ABCC5/MRP5 mRNA levels and resistance to doxorubicin or cisplatin (see abstract and page 3538, col. 1).

Oguri (International Journal of Cancer. 2000. 86: 95-100) detected ABCC5/MRP5 mRNA expression in both normal lung and lung cancer cells in vivo following exposure to carboplatin (page 99). mRNA levels of ABCC5/MRP5 were significantly higher in tissues from patients who had been previously exposed to platinum drugs in vivo than from patients who had not been previously exposed to platinum drugs (page 98, col. 2). The authors also report that ABCC5/MRP5 mRNA levels were not rapidly induced by platinum drugs either in lung cancer cell lines or in PMN cells within 24 hours (see abstract). The teachings of Oguri highlight the unpredictability in the art and the variety of factors which must be considered when interpreting results of screening assays, including time of exposure to an agent, use of cells previously exposed to an agent as compared to cells not previously exposed to an agent, and the relevance of comparing gene expression levels normal cells and cancer cells.

Steinbach (Clinical Cancer Research. 2003. 9: 1083-1086) studied ABCC5/MRP5 mRNA levels in acute myeloid leukemia patients treated with chemotherapy. The authors report that MRP5 mRNA levels were not correlated with survival or remission rate of AML, and thereby are not correlated with response to chemotherapy in AML patients (see abstract, page 1085 col. 2 to 1086 col. 1).

Extensive experimentation would be required to determine whether gene expression levels of each ABCC5, GTF2H2 and ERCC2 are correlated with the occurrence of a representative number of cancers so that one could conclude that a change in the expression level of each of these genes following treatment with an agent is indicative of the therapeutic efficacy of the agent. Extensive experimentation would

also be required to determine whether absolute gene expression levels of each of ABCC5, GTF2H2 and ERCC2 or changes in the gene expression levels of ABCC5, GTF2H2 and ERCC2 are correlated with responsiveness to a representative number of distinct agents. Given that the claims encompass agents having significantly different structures and mechanisms of actions (e.g., agents that are radiation, antibodies, antisense moieties, cisplatin, carboplatin, fluoropyrimidines, etc), it is highly unpredictable as to whether a particular agent will increase or decrease gene expression levels. Extensive experimentation would be required to determine the relevance of a finding that a cancer cell has an increase or decrease in expression of ABCC5, GTF2H2 and ERCC2 following treatment with an agent because the specification has not established that any degree of an increase or decrease in gene expression levels of each of ABCC5, GTF2H2 and ERCC2 is correlated with reduction of cancer cell proliferation, cancer cell death, inhibition of growth of cancer, enhancement or reduction in the onset of cancer or enhancement or reduction in the progression of cancer.

While methods for determining gene expression levels are known in the art, such methods provide only the general guidelines that allow researchers to randomly screen for the effect of an agent on ABCC5, GTF2H2 and ERCC2 gene expression levels. The results of performing such methodology are highly unpredictable, particularly in the absence of an association between ABCC5, GTF2H2 and ERCC2 expression levels and the occurrence of cancer or a general association between ABCC5, GTF2H2 and ERCC2 expression levels and responsiveness to any agent for treating cancer. The

specification has provided only an invitation to experiment. The specification does not provide a predictable means for identifying agents as effective for treating cancer by assaying for the expression of ABCC5, GTF2H2 and ERCC2.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the specification has not enabled one of skill the art to practice the invention as it is claimed because the specification has not established that one can identify an agent that reduces cancer cell proliferation, causes cancer cell death, inhibits growth of cancer, enhances or reduces the onset of cancer or enhances or reduces the progression of cancer by assaying for particular level of expression of each of ABCC5, GTF2H2 and ERCC2 or by assaying for an increase or decrease in the level of expression of each of ABCC5, GTF2H2 and ERCC2 following treatment of any

type of cancer with any type of agent. Although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/
Primary Examiner, Art Unit 1634